Mendel Lecture
Villanova University
January 20, 1996
(Maxine Singer)

It is my hope that these brief remarks will convey to you the deep significance that Gregor Mendel has for me, and other biologists, even now, 130 years after his discoveries. In this way, I hope also to tell you how grateful I am to be receiving this award. For a biologist, having ones name connected with Mendel's is an extraordinary honor.

Mendel's life reminds us that the communal aspects of the scientific endeavor have always been important. Contrary to common prejudice, science is a very social activity. Mendel's monastery, St. Thomas at Brno (Moravia), was a lively intellectual center; biology, part of what was then called natural history, was actively pursued by Mendel and others in that community. Then as now, the scientists were concerned with understanding nature, and also applying that knowledge to practical and economic issues. In the case of St. Thomas' monks, these interests included sheep breeding and wine making and viticulture, the growing of grapes. Mendel could then count on knowledgeable and interested colleagues with whom to discuss his experiments. When Mendel was ready to report his findings to the scientific community outside Brno, he published them in a journal that was received as far away as university libraries in the U.S. That the extraordinary significance of

Mendel's work was not fully appreciated by him, or by other late 19th Century scientists speaks less to their acumen and talents than to the general state of biology at the time. But later, in the first decade of the twentieth century, when that significance became apparent, Mendel's work initiated a level of activity, and a rapid accumulation of understanding that is unabated to this day.

As for Mendel, his later life also exemplifies the experience of many contemporary scientists. His gifts were put to use in the service of his monastery; as Abbot from 1868 until his death in 1884 he was busy with administrative matters, not science.

Just about everyone gets introduced to Mendel in their required school science classes. It's not always a happy experience....Mendel's tall and short, green and yellow, wrinkled and smooth peas don't seem relevant to contemporary concerns. That's a problem caused by poor teaching. Because Mendel matters.

To see why, we can take a look at these wrinkled and smooth peas. In school, you may have seen drawings or diagrams of them. But just 5 years ago, Mendel's wrinkled peas appeared in a photograph on the cover of a scientific journal called Cell. They illustrated one of the papers published there, by a group working in England. The difference between the wrinkled and the smooth peas is a single gene; that gene is normal in the smooth peas but it is mutated, or changed, in the wrinkled ones to a gene which cannot function. The gene is not essential, so the peas are OK, just a little

aged looking. When the gene is functional, as in the smooth peas, the peas are able to make plenty of starch, to plump the peas. When it is not functional, no starch and thus, wrinkles.

Mendel understood that discrete bits of information are inherited through generations of pea plants. Later, these bits were named genes. Mendel understood too that these bits of information could come in different forms---yielding wrinkled or smooth peas, or yellow or green ones. Now, in 1996, genes are no longer abstract entities. We know that genes are portions of DNA molecules that occur in the chromosomes of all living organisms....pea plants and ourselves.

We also now know that different forms of genes, and mutations, are changes in the chemical structure of DNA that alter the encoded information.

Thanks to the ability of late 20th Century geneticists to purify the DNA segments for individual genes, the gene that is changed in the wrinkled plants could be isolated and its structure compared with the normal gene. The change was found to be an insertion, right into the DNA, of an unrelated piece of DNA. This makes it impossible for the plant and its cells to decode the gene's information.

These days, the discovery of such an interrupted gene is not in fact surprising. Moveable DNA segments, what are sometimes called "jumping genes" have been known for 50 years. In the mid-1940s,

even before anyone knew that genetic information is encoded in DNA, or knew the structure of DNA, Barbara McClintock had concluded, that there were jumping genes in corn. It was her studies on the distribution of color on Indian corn kernels that lead to this conclusion. Very few people could follow her experiments or her logic and many either actively disbelieved, or simply ignored the mounting body of evidence she accumulated. Beginning in 1970, however, jumping genes were detected in all kinds of living things, bacteria, insects, other plants, even mammals. This vindicated McClintock and made plain just how profound was her discovery. In the mid-1980s, she received the Nobel Prize.

Until quite recently, it was very difficult to study human genetics because scientists cannot carry out experimental breeding with humans like they can with pease and corn and experimental animals. Geneticists had to count on chance mutations that gave obvious consequences, mainly inherited diseases, and on rare, very large multigenerational families. These investigations made it plain that overall, human genetics works by the same rules that apply to all other organisms, including pea plants. And beginning about 25 years ago, it became possible to study human genes without experimental breeding. Instead, we learned how to isolate genes directly from the human DNA obtained from small samples of human blood cells. Among the many extraordinary consequences of the new techniques, was the demonstration of human jumping genes.

In the mid-1980s, my research group at the NIH began studying some unusual DNA segments in human DNA. These segments did not appear to be regular genes, and the same segment was found a hundred thousand times, peppered among the other genes on human chromosomes. We suspected that these might be jumping genes, but we could not prove that idea. Meanwhile, Dr. Haig Kazazian and his colleagues at Johns Hopkins, were studying boys with the inherited disease, hemophilia A. The inability of hemophilia A patients to clot blood results from mutations in a gene called Factor VIII. Among the boys studied by Kazazian was one who had the disease but whose family had no history of the disease; the illness was the result of a new mutation. When the mutated gene was isolated, it turned out that the Factor VIII gene had an interruption, much like that in the wrinkled pea plants. Here, however, the interruption was by one of those human DNA segments that my lab had been studying. Kazazian's results had proved our speculation. The occurrence of jumping genes in human chromosomes was established.

For the last 5 years, my lab has been doing experiments designed to teach us how this jumping genes moves around. We know now, for example, that this human jumping gene doesn't actually move. Instead, it makes a copy of itself, and moves the copy....something like a FAX machine does. This means, that everytime the jumping gene jumps, there is one more copy of it in our chromosomes. The jumps do not occur very often, but altogether there are about 100,000 copies now in human chromosomes, so it has

been jumping around for a long time. This means that about 5 percent of all the DNA in human chromosomes is made up of these jumping gene segments.

We also know that the jumping genes can move very early in the development of a new human organism, perhaps in the cells that lead to egg and sperm cells. This is learned from studying cells from tumors formed from such cells. Jumping can also occur in the body cells of more mature humans. In at least one case, such a jump has been associated with a mutation linked to the formation of a colon tumor.

As so often happens in research, the study of an unusual phenomenon, wrinkled peas, or the colored markings on corn kernels, has helped us understand very human problems. Jumping genes may once have seemed like a curiosity, and perhaps they seem that way still to some, but like Mendel, they too matter.